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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,049	11/13/2006	David Morritz De Kretser	19721	5961

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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01/22/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,049	DE KRETSER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-16,18-23 and 26-30* is/are pending in the application.

4a) Of the above claim(s) *8,9,13-16,20-22 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,10-12,18,19,23,26 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/26/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/06/2009, is acknowledged.

2. Claims 1, 2, 5-16, 18-23 and 26-30 are pending.

3. Claims 8, 9, 13-16, 20-22 and 27-29 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 are under consideration in the instant application as they read on a method of modulating the inflammatory response/therapeutically and/or prophylactically treating a condition, wherein modulating is downregulation of activin functional activity, achieved by introducing a proteinaceous molecule which functions as an antagonist of the activin expression product, wherein the antagonist is follistatin, and (i) airway inflammation as the specific condition; (ii) an acute inflammatory response; and (iii) targeting activin A.

5. Claim 6 is objected to because it recites "rheumatoid arthritis" twice. Further, the conjunction "or" should be used when listing the species.

6. In view of the amendment filed on 11/06/2009, only the following rejections are remained.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 5-7, 10-12, 18, 19, 23 and 30 stand rejected under 35 U.S.C. 102(b) as being anticipated by US20030162715 for the same reasons set forth in the previous Office Action mailed 05/06/2009.

Applicant's arguments, filed 11/06/2009, have been fully considered, but have not been found convincing.

Applicants submit that the follistatin-like-3 (FSTL3) protein disclosed in the '715 publication, also known as FST-related gene (FLRG) and FST-related protein (FSRP), is not the same protein as follistatin. Applicants take note of the title of the paper by Tortoriello et aL, "Human follistatin-related protein: A structural homotogue of follistatin with nuclear localization (Endocrinology 142:3426-3434, 2001) (attached hereto as Exhibit 2). The reasons for the designation of FSTL3 as a follistatin homologue are provided below. The proteins, FSTL3 and follistatin, are encoded by separate genes, and each is an unique protein which exhibits its own distinct roles, as demonstrated when the gene for each protein is knocked out (see Matzuk et al., Nature 374:360-363, 1995 for fotlistatin knock-out & Muldaerjee et al., Proc Natl Acad Sci USA 104:1348-1353, 2007; attached hereto as Exhibits 3- 4). Although the two proteins have three

follistatin domains with some homology, domain 1 in follistatin contains a heparin binding site that enables follistatin to bind to heparin sulphate proteoglycans on cell surfaces. In contrast, FSTL-3 has a different domain 1 that lacks a heparin binding site and is unable to bind to cell surfaces. In a detailed study of the actions of fotlistatin and FSTL-3, Sidis et al. (Endocrinology 147:3586-3597, 2006) (Exhibit 5) made the following comments regarding the biological activity of the two proteins (see page 3587). These differences are highlighted by the different outcomes when their genes are subjected to targeted disruption. Matzuk et al. (Exhibit 3) report that knock-out of the follistatin gene results in death of all offspring within a few hours after birth due to an inability to breathe, and the pups have abnormal skin as well as whisker mad skeletal abnormalities. In contrast, disruption of the FSTL3 gene is reported by Mukherjee et al. (Exhibit 4), which shows that the mice survive to adulthood, have enlarged islets of Langerhans in the pancreas, reduced visceral fat and enhanced glucose tolerance and increased insulin sensitivity, and also develop hypertension.
Applicant concluded that the disclosure of the '715 publication, which relates to the follistatin-3 protein, is not relevant to the claimed invention involving follistatin. The '715 publication does not teach the claimed invention. Withdrawal of the § 102(5) rejection based on the '715 publication is respectfully requested.

However, the claims are broadly drawn to any activin antagonist including the referenced follistatin-3 protein and are not limited to follistatin as applicant appears to argue. The `715 publication teaches that follistatin-3 protein binds to activin in a dose-dependent manner, wherein it binds to activin A and B (see ¶560&563). The `715 publication teaches the use of follistatin-3 polypeptides in an effort to reduce the activity of a membrane bound receptor by competing with it for free ligand or to bring about a desired response (see ¶338). The `715 publication teaches that follistatins functioning directly as high affinity activin-binding proteins (see ¶3). Follistatin binds stoichiometrically to activins and, as a result, inhibits the activin-induced augmentation of FSH-release from cultured pituitary cells (¶5). Like follistatin-1, follistatin-3 inhibits the secretion of FSH (¶86). Accordingly, Follistatin-3 is considered as activin antagonist.

Claim 26 is not included because Applicant claimed follistatin is not generic to any follistatin and only limited the follistatin described in the specifciation.

9 Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 59 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 03/006057 for the same reasons set forth in the previous Office Action mailed 05/06/2009.

Applicant's arguments, filed 11/06/2009, have been fully considered, but have not been found convincing.

Applicants submit that fibrosis is a different condition from inflammation. Although fibrosis can occur subsequently to inflammation, it is not itself an inflammatory response. Fibrosis is a form of scarring which leads to loss of elasticity of the lung tissue, and is characterized by the deposition of a collagen avascutar matrix in a wound. Although fibrosis is a condition which can

occur subsequently to chronic inflammation, it can also occur in a situation such as fibrinolysis where a fibrin clot, which is the product of coagulation, is broken down. The claimed invention is directed to the treatment of inflammation and not the treatment of fibrosis. These are two distinct conditions. Inflammation can occur without the onset of subsequent fibrosis, and fibrosis can be initiated without a preceding inflammatory response. Accordingly, Applicants respectfully submit that the treatment of fibrosis does not equate to the treatment of an inflammatory response. The disclosure of WO'057, which relates to the treatment of fibrosis, does not anticipate the claimed invention. Withdrawal of the §102(b) rejection based on WO'057 is respectfully requested.

However, the teachings of the WO 03/006057 publication is not limited to fibrosis as applicant argues. The `058 publication teaches the use of follistatin in the treatment of diseases associated with fibrosis such as interstitial lung disease which is airway inflammation. (see page 3, lines 31-33). As is evidence by instant claim 7, that inflammatory response occur in the context of airway inflammation such as interstitial lung disease.

10. The following new ground of rejections are necessitated by the amendment submitted 11/06/2009.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "an activin antagonist" wherein said antagonist is a "proteinaceous molecule" as part of the invention.

However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of an activin antagonist. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

While the specification describes antibodies directed to activin (page 32, line 13), follistatin (page 34), Smad7 antagonist (page 34, line 16), activin subunit βc subunit, activin mutants (page 34, line 24) and soluble activin receptor (page 34). However, there is no described or art-recognized correlation or relationship between the structure of the invention, activin antagonists and it's anti-inflammatory function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of activin antagonists which retain the features essential to the instant invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. Claims 1, 2, 5-6, 10-11, 18, 19, 23, 26 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 8911862.

The WO `862 teaches the inhibin (activin antagonist) is useful in wound healing (see published claim 9), in the treatment of autoimmune diseases (see published claim 3), immunodeficiency diseases (see published claim 1), transplant rejection (see published claims 5, 8), and infection (inflammatory response to bacterial infection) (see published claim 2).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the inhibin polypeptide in the absence of evidence to the contrary.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which inhibin alleviates symptoms of wound healing does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

The reference teachings anticipate the claimed invention.

14. Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 20020192216.

The `216 publication teaches a method of treating inflammation (see published claims 1 and 11), adult respiratory distress syndrome, chronic obstructive airway disorders such as asthma or emphysema (published claim 29), idiopathic interstitial lung diseases (see published claims 7, 26, 41), multiple sclerosis, rheumatoid arthritis (see published claim 9), comprising administering, to a patient in need thereof, a therapeutically effective amount of an inhibitor of a Hedgehog signalling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signalling pathway (see published claim 1), wherein the inhibitor is Follistatin. The `216 publication teaches a method of treating comprising administering, to a patient in need thereof, a therapeutically effective amount of an inhibitor of a Hedgehog signalling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signalling pathway (see published claim 7). Follistatin has been found to inhibit others aspects of BMP activity as well as acting as an activin-binding protein (¶78).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the follistatin polypeptide in the absence of evidence to the contrary.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which follistatin alleviates symptoms of inflammation does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. *In re Baxter Travenol Labs*, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The reference teachings anticipate the claimed invention.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 14, 2010

/Maher M. Haddad/
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